REMARKS

Applicants respectfully requested reconsideration of the instant application in view of the above amendments and the following remarks.

Status of claims

Claims 1-47 are canceled.

New claims 48-59 have been added.

New claims 48-59 are drawn to substantially the same invention as the originally filed claims but are of a different scope than the originally filed claims. Additional support for the new claims can be found throughout the instant specification. In particular, support for the chemical formula of independent claims 48 and 55 can be found, for example, at page 5, line 13 – page 6, line 13. Support for the treatment of inflammatory disorders that involve binding of alpha-9 integrin to an alpha-9 integrin ligand, can be found, for example, at page 3, line 23 – page 4, line 13; page 6, line 26 – page 7, line 6; and page 22, line 20 – page 23, line 3. Support for the list of diseases recited in claim 54 can be found, for example, at page 23, lines 17-24.

The new claims place the application in better condition for allowance, *inter alia*, because they are drawn to a specific category of compounds having a defined chemical structure for a particular end use, *i.e.*, treating inflammatory disorders associated with alpha-9 integrin binding to alpha-9 integrin ligand.

No new matter has been added by these amendments.

Responses to rejections (generally)

In view of the above claim amendments, which canceled the original claims and added new claims 47-58, Applicants submit the rejections set forth in the Office Action of January 8, 2004 are now moot. However, in the interest of expediting prosecution, Applicants will address

the rejections as though they were asserted by the Patent Office against one or more of the new claims. Where Applicants believe the rejections could not be applied to the new claims, Applicants reasoning will be provided.

Rejection under 35 U.S.C. § 112, first paragraph

A. Original claim 39 (now canceled) was rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to convey to one skilled in the art that Applicants had possession of the invention. Specifically, the Office Action alleged that while certain portions of the specification "pertain to the binding between alpha-9 and the cited proteins," there is no descriptive support for "binding between an alpha-9 antagonist and the cited proteins." Office Action at page 2.

Applicants submit that this rejection would not apply to the new claims. New claim 47, from which new claims 48-54 depend, is drawn to a "method of treating inflammatory disorders ... [that] involves binding of alpha integrin to a alpha-9 integrin ligand." New claim 55, from which new claims 56-59 depend, is drawn to "a method of inhibiting binding of an alpha-9 integrin to an alpha-9 integrin ligand." Accordingly, the new claims do not recite "binding between an alpha-9 antagonist and the cited proteins" or claim a method drawn to such binding. Since the written description rejection appeared to be specifically directed to an alleged lack of support for binding between an alpha-9 *agonist* and the cited proteins, it would not appear to be relevant to the new claims.

B. Claims 31-40 and 47 were rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement, because the specification allegedly does not provide experimental data showing that the antagonists of the claimed methods are effective in antagonizing alpha-9 integrin.

To support the rejection, the Office Action cited several references, which apparently reported the presence of inactive species within certain genera of VLA-4 inhibitors. The Office Action reasoned that since the structure/activity of putative VLA-4 antagonists is unpredictable,

and since Applicants have predicted alpha-9 integrin antagonism based on the ability of the antagonists of the claimed methods to antagonize VLA-4, there must also be unpredictability in the structure/activity of the antagonists of the claimed methods to inhibit alpha-9 integrin. Office Action at page 3.

Inasmuch as this rejection could be asserted against one or more of the new claims, Applicants submit that this argument is misplaced, both legally and scientifically. To establish a *prima facie* case for lack of enablement, the burden is on the Patent Office to provide objective evidence to dispute the enablement provided by the specification and to explain why it doubts the truth or accuracy of the disclosure. *In re Marzocchi*, 439 F.2d 220, 224 (CCPA 1971); *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993).

In this case, the Patent Office has apparently overlooked or ignored the teachings of the specification, which provides greater guidance than the language of the instant rejection would suggest. The instant specification imputes alpha-9 integrin antagonism based, *inter alia*, on empirically-determined data with respect to VLA-4 antagonism. Therefore, the level of unpredictability that may exist in the area of VLA-4 antagonist structure-function is not relevant since the relevant VLA-4 antagonists have been identified experimentally, thereby traversing any perceived scientific hurdle with respect to VLA-4 antagonist structure-function predictions. See, *e.g.*, Specification at page 5, lines 1-8; page 7, lines 7-12; page 9, lines 17-24; page 13, line 16 – page 15, line 8; page 17, line 14 – page 19, line 9 (including Table 1); page 22, lines 3-9; page 29, lines 22-26; and Example 1.

There is also support for Applicants' assertion that compounds that modulate the binding of α-4/β-1 integrin (such as VLA-4) to its ligands are generally good candidates for modulating the binding of alpha-9 integrin to its ligands. Specification at, *e.g.*, page 13, line 29 - page 14, line 5. Thus, Applicants assertion of utility in the instant invention is not based merely on the structure of the claimed compounds, as apparently set forth in the Office Action. Rather, Applicants' assertion of utility is based on empirical evidence of VLA-4 binding in view of what is known about the relationship between α4/β1 ligands and alpha-9 ligands.

The Office Action further stated that while, "many of the compounds that fall within the scope of claim 35 will exhibit an IC_{50} of 15 *micro*molar in an assay of VLA-4 . . . [n]o correlation has been established between this . . . parameter, and successful treatment of Alzheimer's disease, [etc.]." The Office Action cited *Ex parte Foreman* and *In re Wands* for factors to be considered in determining whether undue experimentation is required to practice the invention. *Ex parte Foreman,* 230 USPQ 546 (Fed. Cir. 1986); *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Again, the Patent Office appeared to place significant weight on published reports of "failure" in the treatment of inflammatory conditions to support he proposition that treatment of the diseases recited in the claims was not enabled by the specification.

Applicants recognize that "failure" is part of the scientific process. Applicants need not articulate what those skilled in the art know so well. Yet, by its statements, the Patent Office appears to be asserting that prior reported failures in a particular area of research may be used as objective evidence to challenge Applicants' disclosure. Office Action at page 8. No doubt, a large number of compositions, or method of use thereof, have failed to treat certain human diseases, disorders, and/or conditions. However, precluding patentability of novel compounds in view of the failure of others would lead to absurd results in virtually all areas of patent practice. Applicants' invention is novel in view of the prior art, which necessary requires that Applicants have overcome certain limitations in the prior art.

Here, Applicants have already established that 373 compounds have an IC_{50} of 100 μm, or less, with respect to VLA-4 binding and that binding to VLA-4 is predictive of binding to alpha-9 integrin. Specification at, *e.g.*, page 18, line 6 – page 19, line 8. Furthermore, Applicants provided drug screening assays (Examples 1 and 2 and pages 29-30), an animal model (Example 3), and synthesis methods (Example 4), to allow one skilled in the art to identify compounds that modulate the binding of alph-9 integrin to its ligands.

The language of the rejection also appeared to require that Applicants provide experimental evidence of the treatment of certain diseases and address issues related to bioavailability and pharmacokinetics. Office Action at page 5. By making such a requirement,

the Patent Office would essentially preclude patenting of a compound until it had been evaluated in advanced clinical studies. This has never been the law for patenting small molecule pharmaceutical compounds. By requiring a patent applicant to provide such data, in exchange for patent protection, the Patent Office would force inventors to delay applying for patent protection until late in the drug discovery process, once significant financial capital has been invested in a drug. From a policy standpoint, Applicants submit that drug discovery would be adversely affected if patent protection was only available after such an enormous expenditure. Moreover, Applicants are well aware that it is not typical for the Patent Office to require pharmacokinetic and bioavailablity data for the patenting of novel pharmaceutical compounds. Accordingly, the basis for the instant enablement rejection is inconsistent with both PTO policy and practice.

Determining the level or experimentation routinely required in the relevant art is one of the Wands factors. *Wands*, 858 F.2d at 737. However, the test for routine experimentation is not quantitative, nor are time and expense to be considered controlling factors. *Id.* at 737; *United States v. Telectronics, Inc.*, 857 F2d 778, 785 (Fed. Cir. 1988). Experimentation in the biological sciences can take many years, cost a considerable amount of money, and require numerous skilled personnel. Nonetheless, such experimentation may be entirely routine in terms of methods and reagents. The Office Action's suggestion that Applicants "undertake the experimentation they view as routine" is well-taken and underscores the time, cost, and effort associated with research in the biological sciences. However, the statement does not change the fact that "routine experimentation" in the biological sciences may be labor-intensive and time-consuming. Where the specification is otherwise enabling to allow one skilled in the art to make or practice the invention, the amount of experimentation necessary to make or practice the invention must be viewed in the context of the relevant art. *Wands*, 858 F.2d at 737; *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993).

Applicants therefore submit that the Office Action failed to establish a *prima facie* case for lack of enablement, with respect to the originally filed claims (now canceled), for Applicants

to rebut. Applicants further submit that a similar rejection, if asserted against one or more of the new claims, will fail for similar reasons.

Rejections under 35 U.S.C. § 112, second paragraph

In view of the cancellation of the original claims, Applicants submit that these rejections are now moot.

Rejection under 35 U.S.C. § 102(e)

Claim 33 stands rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Lin (U.S. Patent 6,248,713). The Office Action, at page 11, appears to allege that claim 33 has alternative interpretations, one of which would render it "anticipated by any reference that discloses an alpha 4 antagonist. Office Action at page 11.

Claim 33 (now canceled) recited "[t]he method of Claim 31, wherein said alpha-9 integrin antagonist compound is a [*sic*] selected from a group of compounds which inhibit alpha-4/beta-1 integrin binding to an alpha-4/beta-1 integrin ligand."

Despite the cancellation of claim 33, Applicants address this rejection should it be asserted against any of the new claims, for example, claim 50 and/or claim 57.

The most reasonable interpretation of claim 33 (now canceled) is that the method claim requires a compound that is an alpha-9 antagonist *and* is selected from the group consisting of alpha-4 antagonists. This interpretation corresponds to interpretation (a) on page 11 of the Office Action.

Interpretation (b) of the Office Action is not supported by the language of the claim because there is no indication that alpha-4 antagonists are *necessarily* alpha-9 antagonists. The alpha-9 antagonists to be used according to the recited methods are merely *selected from* alpha -4 antagonists. Using the logic of interpretation (b), any claim reciting a compound or element selected from a certain group of compound or elements that have other known uses could be

interpreted to mean that all the member of the group were inherently useful for the claimed use. Applicants, therefore, submit that interpretation (b) is improper.

Accordingly, the plain language of amended claim 33 does not indicate, explicitly or implicitly, that the property of being alpha-9 integrin antagonists is inherent in or co-extensive with the property of being an inhibitor of alpha-4/beta-1 integrin binding to an alpha-4/beta-1 integrin ligand. For at least this reason, the rejection under 35 U.S.C. § 102(e) is improper with respect to claim 33 (now cancelled), and would be improper if asserted against one or more of the new claims.

Rejections under 35 U.S.C. §103

A. Claims 31- 47 stand rejected under 35 U.S.C. § 103 as allegedly being unpatentable in view of Smith (J. Biol. Chem. 271:28485, 1996). Specifically, the Office Action appears to assert that Smith *et al.* disclose that osteopontin binds to alpha-9 integrin; therefore osteopontin is an alpha-9 antagonist, and since one skilled in the art would expect that all alpha-9 antagonists will be effective in treating an alpha-9-associated disease, claims 31-47 (particularly claims 37 and 44) are rendered obvious. Office Action at pages 12-13.

Inasmuch as this rejection could be asserted against one of more of the new claims, Applicants traverse the rejection.

It is black letter patent law that to establish a prima facie case for obviousness, the prior art reference(s) must teach each and every limitation of the claim(s) alleged to be obvious and must provide a reasonable probability of success. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). Applicants' disclosure cannot be used to fill deficiencies in the prior art. *Id.*

Here, the Patent Office based the obviousness rejection on a single reference, Smith *et al.*, which does not teach all the limitation of the relevant claims. While Smith *et al.* identified alpha-9 as the subunit responsible for osteopontin binding (pages 28488-89), they did not appear to recognize that alpha-9 is associated with disease. Smith *et al.* appear to recognize that alpha-9

is expressed on most epithelial cells and that osteopontin expression appears to be upregulated "at the interface between malignant and normal tissue." Page 28490. Smith *et al.* then speculate that it "would be interesting if α_9 is coordinately up-regulated at these sites." *Id.*

It is clear from reading the Smith *et al.* paper that the function of alpha-9 was unknown and the effect of osteopontin binding to an integrin comprising an alpha-9 subunit was unknown. Accordingly, Smith *et al.* do not teach the use of alpha-9 to treat any disease and, therefore, do not teach each and every limitation of the instant claims. Thus, the Patent Office has not established a *prima facie* case for obviousness for Applicants to rebut. For at least these reasons, the rejection should not be reiterated in response to the new claims.

Claim 45 was also rejected for reasons relating to its apparently-alleged dependency on claim 44. Office Action at pages 12-13. Claim 45 depended from claim 41. Neither claim 41 nor claim 45 depended from claim 44 (all three claims now canceled). Accordingly, there was no legal basis for incorporating limitations of claim 44 into claim 45, as asserted in the Office Action. In view of the cancellation of the original claims, Applicants address this rejection only because it is inconsistent with black-letter law with respect to claim interpretation and has no legal basis. Accordingly, Applicants wish to avoid having to address a similar rejection as applied to one or more of the new claims.

B. Claims 31- 47 stand rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Palmer *et al.* (J. Cell Biol. 123:1289, 1993). Specifically, the Office Action alleges that "given the involvement of alpha-9 in various diseases, any antagonist of alpha-9 will be effective to mitigate symptoms of the disease." Page 13.

Inasmuch as this rejection could be asserted against one or more of the new claims, Applicants traverse the rejection because, *inter alia*, the explicit teachings of the Palmer *et al.* paper do not support the rejection. The Palmer *et al.* paper describes three novel findings, which are summarized at page 1294: (i) the cloning and sequencing of alpha-9, (ii) heterodimer formation between alpha-9 and beta-1 integrin subunits, and (iii) a widespread expression pattern

for alpha-9, including expression in airway epithelial, basal squamous epithelial, smooth and skeletal muscle, and hepatocyte cells. Palmer *et al.* speculate that "α_9 may be involved in homotypic cell-cell interactions" and conclude their study by stating that

> this study demonstrates the existence of a previously unrecognized member of the integrin family that is widely expressed in vivo in differentiated cells that are not actively involved in migration, proliferation, or heterotypic interactions with other cells. More definitive functional characterization of will require identification of the ligand or ligands for this receptor and the development of reagents that specifically interfere with its function.

Page 1296. Accordingly, while the paper discloses that alpha-9 is more closely related to alpha-4 (39%) than other integrins (18-22%; *see, e.g.*, page 1292), Palmer *et al.* do not impute properties of alpha-4 to alpha-9. Instead, Palmer *et al.* conclude that alpha-9 has unique biological properties that are distinct from alpha-4. Furthermore, Palmer *et al.* do not disclose that alpha-9 is involved in disease.

Thus, the assertion in the Office Action that "given the involvement of alpha-9 in various diseases, any antagonist of alpha-9 will be effective to mitigate symptoms of the disease," is not supported by the reference because no such teaching is "given" by the Palmer *et al.* paper.

Since the Palmer *et al.* paper does not teach each and every limitation of the claims in question, as required by *In re Vaeck*, and the Patent Office has failed to establish a *prima facie* case to support its obviousness rejection. For at least these reasons, a similar rejection should not be reiterated with respect to the new claims.

C. Claims 31- 47 stand rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Lin (U.S. Patent 6,248,713) in view of Palmer *et al.* (J. Cell Biol. 123:1289, 1993). Specifically, the Office Action alleges that Lin discloses compounds that antagonize VLA-4 and Palmer *et al.* disclose structural homology between alpha-4 and alpha-9 integrin subunits, rendering obvious compounds that antagonize alpha-9. Page 14.

Inasmuch as this rejection could be asserted against one or more of the new claims, Applicants traverse the rejection. As described above, Palmer *et al.* teach away from the idea that the 39% homology between alpha-4 and alpha-9 is reason to impute the biological characteristics of alpha-4 to alpha-9. It is improper for the Patent Office to select portion of the Palmer *et al.* reference to support an obvious rejection, where the reference as a whole teaches away from the claimed invention. Thus, for reasons similar to those set forth above, Applicants submit that the Palmer *et al.* paper, either alone or in view of Lin, does not teach each and every limitation of the claims in question, as required by *In re Vaeck.*

The Patent Office has failed to establish a *prima facie* case to support its obviousness rejection, which would presumably be similarly improper if asserted against one or more of the new claims.

D. Claims 31- 47 stand rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Yokosaki *et al.* (J. Biol. Chem. 169:26691-96, 1994). Specifically, the Office Action appears to assert that

(1) Yokosaki *et al.* discloses that tenascin binds to alpha-9 and one skilled in the art would recognize that tenascin could be used as an alpha-9 antagonist to treat alpha-9-mediated diseases (pages 14-15) and

(2) since, in Applicants claims, alpha-9 could presumably be in a [hetero]dimer along with beta-1, an antibody specific for beta-1 would qualify as an alpha-9 antagonist within the meaning of the claims. Based on this reasoning, the beta-1-specific antibody disclosed in Yokosaki *et al.* renders obvious the claimed alpha-9 antagonists for use in treating alpha-9-mediated diseases (page 15).

Applicants traverse both rejections should they be asserted against one or more of the new claims. With respect to (1), Applicants submit that Yokosaki *et al.* do not disclose that alpha-9 is associated with any disease. Therefore, even if one skilled in the art recognized that tenascin, an alpha-9 ligand, could also be an alpha-9 antagonist, Yokosaki *et al.* does not teach that the use of

an alpha-9 antagonist is useful for the treatment of disease. Accordingly, Yokosaki *et al.* fails to teach each and every limitation of the instant claims and cannot be used to support a prima facie case of obviousness under the standard of *In re Vaeck*, as described above.

With respect to (2), Applicants submit that the instant specification explicitly excludes beta-1-specific antibodies as potential alpha-9 antagonists according to the invention. The specification identifies numerous types of compounds for testing as alpha-9 antagonists, "including small molecules, including peptides and peptidomimetics . . . candidate compounds from combinatorial libraries, fermentation broths and lysates, phage libraries, and the like..." Page 13, lines 5-9. Small molecules are further described at page 14, line 5 – page 16, line 11, with particular emphasis on synthetic peptides or peptide mimetics identified using high-throughput screening. Table 1 provides examples of antagonists, none of which are antibodies. These compounds are described as being "selective for alpha-9 integrin activity, *as opposed to* $\alpha_5\beta_1$, $\alpha_4\beta$ or $\alpha L\beta_2$ activity." Page 21, lines 7-9, emphasis added. Such compounds would necessarily exclude antibodies to β_1, which would presumably bind to $\alpha_5\beta_1$ heterodimers, thereby defying the explicit teaching found in Applicants' disclosure.

Accordingly, Applicants submit that the instant specification teaches against the use of compounds that would recognize the β_1 integrin subunit or heterodimers comprising the β_1 subunit. Therefore, one skilled in the art would not give the claims the meaning proposed in the Office Action and there is no basis for the obviousness rejection. For at least this reason, the rejection would not stand against claims 31-47 (now canceled) and, for similar reasons, should not be asserted against the new claims.

CONCLUSION

Applicants believe that the instant application is now fully in condition for allowance. Early notice to that effect is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872.

Respectfully submitted,

Date: April 30, 2004

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